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The Role of Sexual Transmission of HIV Infection Among Injection and Non–Injection Drug Users

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ABSTRACT *Many early studies of injecting drug users (IDUs) suggested that most HIV infections in this population were due to needle sharing and that sexual transmission was negligible or was overshadowed by parenteral routes. A few of the early studies suggested a potentially important role for heterosexual transmission, but these tended to be limited to cross-sectional data or had only a few years of prospective follow-up. Studies of sexual risk factors for HIV infection among non–injecting drug users (NIDUs) are similarly sparse. Recently, investigators prospectively examined both drug-related and sexual risk factors for HIV seroconversion among male and female IDUs with an adequate number of person-years to identify statistically significant associations. Other studies among never and former IDUs have identified associations suggesting that sexual transmission accounts for a substantial number of HIV seroconversions in these populations. Herein, highlights are discussed from recent investigations among IDUs in Baltimore, Maryland, and corroborating findings from the literature. Results from a 10-year prospective analysis of the ALIVE study and an analysis of the REACH studies spanning a 7-year period indicate that sexual risk factors for HIV infection are important in both female and male IDUs. These findings underscore the need for HIV interventions among drug users that incorporate sexual risk reduction. Based on the existing literature, a narrow focus on injection-related risks is an ineffective prevention strategy. Interventions that target specific subgroups of high-risk IDUs, such as men who have sex with men and inject drugs (MSM-IDUs), sex worker-IDUs and HIV-infected IDUs, deserve special attention.*

KEYWORDS *HIV/AIDS, Injection drug use, Sexual risk behavior, HIV interventions for drug users.*

STUDIES OF SEXUAL HIV TRANSMISSION AMONG IDU POPULATIONS

In early landmark studies of injecting drug user (IDU) populations, most HIV infections appeared to be due to parenteral risks[1–3] leading to the presumption that sexual risks among IDUs were negligible. Other studies suggested that sexual risks were present, but were overshadowed by parenteral risks.[4–6] In addition, field observations indicated that although many IDUs were comfortable with recalling injection behaviors in vivid detail, they were often modest or embarrassed when inter-

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viewed about sexual behaviors (personal communication, Dr. David Vlahov). As injection risks have declined over time, investigators have learned to approach sexual questions with greater sensitivity, for example using new technology such as audio-computer assisted self-interview (A-CASI). The use of A-CASI has been associated with increased reporting of sexual and drug-using risks among IDUs,[7–9] which suggests that future studies incorporating these methods will have greater validity.[9]

In the 1990s, a few cross-sectional studies reexamined sexual behaviors as correlates of HIV infection among IDUs and found that they had a potentially important role.[10,11] A national survey of females with IDU partners also highlighted the potential for women to acquire HIV through sexual transmission.[12] However, only in recent years have prospective studies of IDUs accumulated adequate follow-up and commensurate statistical power to disentangle the effects of drug use versus sexual risk factors, taking into potential gender differences.[13,14] We highlight some of these findings from three analyses derived from a longitudinal cohort study of IDUs (ALIVE); a cohort study of young, newly initiated injection and non–injection drug users (REACH III); and a combined analysis of three cohorts of young, newly initiated injection drug users (REACH I, II, and III). Corroborating studies and areas for future research are also discussed.

ALIVE Cohort

From 1988 to 1989, a total of 2,946 persons who were at least 18 years old were recruited into a longitudinal study of the natural history of HIV infection in IDUs in Baltimore, called the AIDS Link to Intravenous Exposure (ALIVE). At study enrollment, 25% of participants were HIV-infected.[15] To be eligible for this analysis, participants were required to be HIV seronegative at enrollment and to have returned for at least one follow-up visit. HIV seroconverters for whom there was more than a 3-year interval between their last HIV-negative and first HIV-positive test were also excluded (24 of 301 seroconverters). Therefore, a total of 1,874 persons were studied from 1988 to 1998. Semiannual interviews collected data on drug use history, sociodemographics, and drug use and sexual behavior within the previous 6 months. At each study visit, HIV seroconverters were identified by commercial HIV antibody enzyme-linked immunosorbent assay (ELISA). Repeatedly seropositive specimens were confirmed by Western blot.

Poisson regression was used to calculate relative incidence for exposure variables per semiannual period over the 10-year study period, stratified by gender. Behavioral data and variables reflecting use of specific services within the previous 6 months (e.g., attendance at needle exchange programs [NEPs] and methadone maintenance) were treated as time-dependent covariates that were subsequently updated for each semiannual period. To assess whether HIV incidence and specific risk factors differed for male and female IDUs, Poisson regression models were constructed, stratifying by sex. To take into account temporal trends in HIV seroconversion, we adjusted for calendar year. Details on these analytic methods are described elsewhere.[14]

Among a total of 8,826.45 person years (PY) of observation, 277 documented HIV seroconversions occurred, for a global HIV incidence rate of 3.14 per 100 PY (95% confidence interval [CI], 2.78–3.53). HIV incidence declined significantly over time from 4.58 per 100 PY in 1988 to 1.29 per 100 PY in 1998; this translated to a 10% decrease per year. The rate ratio for HIV seroconversion among women versus men was 1.04 (95% CI, 0.8–1.4).

After taking into account multiple time-dependent risk factors for HIV infection, younger age was the only risk factor that remained independently associated with the risk of HIV seroconversion for both men and women. IDUs who were younger than 30 years at enrollment were more than twice as likely to undergo HIV seroconversion. Among men, independent predictors of HIV seroconversion included sociodemographic, drug-related, and sexual risks. Having achieved at least a high school education was inversely associated with HIV seroconversion, whereas injecting daily or more, injecting cocaine, and attending shooting galleries were associated with an increased risk of HIV transmission. Male IDUs recently engaging in homosexual activity were more than twice as likely to seroconvert compared with those who reported no recent homosexual contact, whereas men reporting one or more heterosexual partners were almost half as likely to seroconvert compared with those reporting no recent heterosexual partners.

Among female IDUs, no drug-related variables associated with HIV incidence in univariate models retained statistical significance after taking into account other risk factors. After adjusting for the effects of age and time, female IDUs having a recent sexually transmitted disease (STD) increased the risk of HIV seroconversion more than 2-fold (rate ratio, 2.52; 95% CI, 1.39–4.58). Having a male sex partner who was also an IDU was marginally associated with HIV seroconversion among females.

These findings suggested that sexual risks were important risk factors for HIV seroconversion among both male and female IDUs, and that risk factors differed markedly by gender. Based on these findings, we concluded that interventions targeted toward IDUs should take into account sexual risks and be gender specific. Details on these results are included in a previously published report.[14]

REACH Cohort

The ALIVE study findings led us to investigate whether sexual HIV risks also factored prominently among younger IDUs who tend to be more sexually active. We compared baseline data from 409 IDUs and 165 NIDUs from the REACH III Study, all of whom were aged 15 to 30 years and who initiated use of cocaine, heroin, or crack within the previous 5 years. Interestingly, HIV prevalence was nearly identical among the IDUs and NIDUs (4.40% vs. 3.64%, $P = .67$, respectively), whereas hepatitis C virus (HCV) antibody prevalence differed markedly (55.23% vs. 3.04%, respectively) (unpublished data). Since HCV prevalence is a well-known marker of high-risk injection practices and is 10-fold more infectious than HIV through the parenteral route, we would have expected higher rates of HCV prevalence among NIDUs if some of these persons had failed to admit to a history of injection drug use. However, in this sample there were no HIV-HCV coinfections, which lends credence to the notion that their self-reported risk behaviors were valid. Interestingly, the prevalence of syphilis antibodies among IDUs and NIDUs was 1.48% and 4.38%, respectively ($P = .04$), suggesting a potentially important role of sexual transmission of STDs and HIV among NIDUs.

REACH Mega-Project

To investigate the robustness of our findings among young IDUs and over time, we constructed a data set comprising three cross-sectional waves from young IDUs in Baltimore from 1994 to 2002.[16] For this analysis, only IDUs aged 18 to 30 years were included who had first injected drugs within the prior 5 years. Subjects who participated in more than one of the above studies were included only once. Over-

all, HIV prevalence was higher in females than in males (12% vs. 6%, $P = .009$) and African Americans versus Caucasians (14% vs. 4%, $P < .001$). Although the number of males who reported having sex with other males was low, these men had much higher HIV prevalence rates compared to those who had not engaged in sex with other males (47% vs. 8%, $P < .001$). Among persons who had less than 1 year between their first use of crack, heroin, or cocaine and their first injection, HIV prevalence was also much higher compared to those with longer periods of transition to injection drug use (17% vs. 8%, respectively, $P = .018$). Additionally, HIV prevalence steadily declined over the three study waves ($P < .001$).

Logistic regression was then used to assess factors independently associated with prevalent HIV infections. After stratifying by gender, preliminary analysis indicated that independent correlates of HIV infection among males (N = 327) included being African American, younger, having had sex with another male, and having shared needles in the past 6 months. Having a shorter duration from non–injection drug use to injection drug use and having injected cocaine or speedballs were marginally associated with HIV infection. Among females (N = 345), a different set of correlates emerged. In this case, younger age and having injected speedballs or cocaine were the only risk factors female IDUs held in common with males. However, having an IDU sex partner, having had an STD, and having first had sexual intercourse before the age of 15 were also independently associated with HIV infection. Both multivariate models were adjusted for time to avoid bias due to secular trends.[16]

Taken together, these analyses echo findings from the ALIVE study and suggest that sexual behaviors may be important throughout the trajectory of an injection drug-using career. However, since this analysis was based on cross-sectional data, temporal inferences cannot be drawn. Prospective studies are needed to characterize the role of sexual behaviors in HIV transmission among younger cohorts of IDUs.

DISCUSSION

A number of other studies support the findings reported above. In particular, the San Francisco Urban Health Study[13] found that similar sexual risks among male and female IDUs were observed over a 10-year period. In the latter study, women who had engaged in prostitution were found to be at higher risk of HIV seroconversion, as were men having sex with men who also injected drugs (MSM-IDUs). More recently, Page-Shafer and colleagues confirmed a strong association between homosexual/bisexual activity and HIV seroconversion among young IDUs in San Francisco.[17]

In some cases, women IDUs have been found to have higher rates of HIV seroconversion than men. Earlier in the ALIVE study, we found that the risk of HIV seroconversion among women IDUs was 2-fold higher relative to men over 5 years of follow-up.[18] However, with an additional 5 years of follow-up, these gender differences in HIV incidence disappeared.[14] The reasons for this are unclear. Recently, in Vancouver, Canada, Spittal and colleagues[19] reported that women IDUs had higher rates of HIV seroconversion than men. HIV incidence was particularly high among female IDUs who were Aboriginal (i.e., First Nations, Inuit, or Métis).

Although previous studies have documented high levels of risk behaviors among MSM-IDUs,[20–23] small sample size precluded the ability to demonstrate the significantly elevated HIV incidence that MSM-IDUs experience relative to heterosexual male IDUs. The above studies now clearly indicate that homosexual behav-

ior is an independent risk factor for incident HIV infections among male IDUs and confirms earlier findings that interventions are needed to specifically meet the needs of this subgroup.

Recent studies of NIDUs have highlighted the potential for sexual transmission to occur among this population.[24,25] Neaigus et al.[24] reported that never-injectors infected with HIV and hepatitis B virus (HBV) appeared to have become infected mainly through sexual transmission. In the same study, former IDUs appeared to have become infected with HIV and HCV mainly through injecting risk, and with HBV through both injecting and sexual risk. The opportunity for NIDUs to act as a bridge of infection to the general population has been acknowledged. NIDUs and members of their social networks may be unaware of each other's drug use and other risk behaviors.[24]

Data on NIDUs have not all been consistent; however, Poulin et al.[26] examined the prevalence of STDs among 738 female drug users attending an STD prevention clinic and NEPs in Quebec City, Canada, and found that IDUs were more likely to have had a history of STDs than NIDUs. IDUs also had a significantly higher prevalence rate of HIV than NIDUs (8.9% vs. 6%), but there were no differences in the prevalence of current gonorrhea and chlamydia between the IDUs and NIDUs (3.5% vs. 4.2%).

Studies have shown that women tend to have more overlap between members of their drug use and sexual networks relative to men,[27,28] making female drug users especially vulnerable to acquiring HIV and other STDs through unprotected sex. A recent article by Miller and Neaigus[28] reported that, among male NIDUs, increased sex risk was independently associated with support from sex partners, whereas among female NIDUs, increased sex risk was independently associated with having used heroin with sex partners. This study concluded that social support from sex partners can have both positive and negative effects on HIV risks among drug users. Types of partnerships may also influence sex risks among drug users. In particular, women drug users who trade sex are reported to have high levels of condom use with their clients, but not with boyfriends,[29] despite the fact that the latter may pose a higher risk of infection.

FUTURE DIRECTIONS

These studies indicate that sexually acquired HIV infections between IDUs, NIDUs, and their sexual partners are an important dynamic in the HIV/AIDS epidemic that remains poorly understood. The fact that findings among IDUs have been consistent across cities with both low (i.e., San Francisco) and high HIV prevalence among IDUs (i.e., Baltimore, New York City) lends support for this hypothesis. However, additional research is needed to understand the attributable and relative risks of injection drug use versus sexual risk behaviors and whether these remain stable by gender; across age groups, social networks, and time periods; and throughout an injection drug use career. If these risks differ, the underlying mechanisms accounting for these findings may have important implications for scaling up specific types of interventions at different points in the epidemic, or to reach different subpopulations of persons at risk.

Research is also needed to determine whether and how HIV interventions work for specific subgroups of drug users that are known to be at high risk of infection, such as MSM-IDUs, female IDUs, ethnic minority IDUs, noninjecting IDUs, and sex worker IDUs. Related to this is the question of whether interventions aimed at

HIV-seronegative IDUs are equally or more effective than those targeted toward HIV-seropositive IDUs, especially in high-prevalence settings. Such findings will have implications for policymaking decisions and direct relevance for research on other blood-borne infections, such as HCV.

Several reports from developing countries and states, such as Burma (Myanmar), Manipur, and most recently, Ukraine[30,31] have documented IDU-associated HIV epidemics that spread to the general population chiefly through heterosexual contact. In each of these regions, HIV prevalence among the general population exceeds 1% and originated principally from injection drug use. Countries including Vietnam, Kazakhstan, Moldova, Russia, and China are at risk of repeating the same experience unless effective interventions are introduced on an appropriate scale without further delay.

The circumstances that lead some HIV epidemics among IDUs to remain localized and others to become generalized are not well understood. Such factors as sexual mixing between IDU sex workers and clients, paid blood donations, high rates of ulcerative STDs, bisexuality, and incarceration have been identified as being likely to play a role.[31] The maturity of the HIV epidemic among IDUs and among heterosexuals in some regions is thought to have influenced the generalization of the epidemic in parts of Asia.[32] Although the United States has not experienced the dramatic HIV spread from IDUs to the general population witnessed in these countries, there is potential for this situation to occur. Efforts to understand the dynamics of the HIV epidemic and to evaluate interventions that stem from both injection-related and sexual transmission risks are of utmost priority.

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